#### IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT: DANETTE A. DUDLEY, ET AL. EXAMINER:

SERIAL NO: ART UNIT:

FILED: PAPER NO:

FOR : QUINOXALINONES AS SERINE PROTEASE INHIBITORS SUCH AS

FACTOR XA AND THROMBIN

#### PRELIMINARY AMENDMENT

January 4, 2002

# BOX PATENT APPLICATION Commissioner for Patents Washington, D.C. 20231

Dear Sir:

This is a Preliminary Amendment for a Utility (Divisional) Application based on U.S. Patent Application Serial No. 09/601,606 filed August 3, 2000.

Please enter the following amendments and remarks in the present application.

## IN THE SPECIFICATION:

On page 1, after the title, please insert:

- CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of USSN 09/601,606 filed August 3, 2000, now allowed, which is a 371 filing of PCT/US98/26704 filed December 15, 1998, having benefit of Provisional Application No. 60/080,042 filed March 31, 1998. --

## IN THE CLAIMS:

Claim 1 (amended). A compound according to Formula I

Express Mail No. EF378134428US

$$L \xrightarrow{X_3} X_4 \xrightarrow{A} D \\ X_2 \xrightarrow{X_1} F E$$

or stereoisomers or pharmaceutically acceptable salts, esters, or amides, wherein:

A is selected from NCH<sub>2</sub>, N(alkyl)CH<sub>2</sub>, CH<sub>2</sub>N, CH<sub>2</sub>N(alkyl);

B is selected from H,  $(C_{3-20})$ alkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, each optionally substituted with  $R_1$  and  $R_2$ ;

D is selected from H,  $(C_{3-20})$ alkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, each optionally substituted with  $R_1$  and  $R_2$ ;

E is absent or selected from O, S, NH;

F is selected from N, NCH<sub>2</sub>, CH<sub>2</sub>N;

- G is absent or selected from alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl, cycloalkyl interrupted by one or more heteroatoms;
- J is absent or selected from aryl or heterocycle each optionally substituted with  $R_1$  and  $R_2$ ;
- K is absent or selected from an alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl interrupted by one or more heteroatoms, cycloalkylalkyl interrupted by one or more heteroatoms, each optionally substituted with R<sub>1</sub> and R<sub>2</sub>;
- L is selected from H, chlorine, fluorine, bromine, iodine, OH, O(alkyl), amine, alkyl, fluoroalkyl, amide, NO<sub>2</sub>, SH, S(O)<sub>n</sub>(alkyl), SO<sub>3</sub>H, SO<sub>3</sub>alkyl, aldehyde, ketone, acid, ester, urea, Oalkylamide, Oalkylester, Oalkylacid, Nalkylacid, alkylamine, alkylamide, alkylketone, alkylacid, alkylester, alkylurea, Nalkylamide,

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Nalkylester, NC(=O)alkyl, NC(=O)aryl, NC(=O)cycloalkyl, NC(=O)cycloalkylalkyl, NC(=O) alkylaryl, R<sub>1</sub>, R<sub>2</sub>, nitrile;
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R<sub>1</sub> is selected from H, amine, alkylamine, amide, C(=NH)NHNH<sub>2</sub>,
alkylC(=NH)NHNH<sub>2</sub>, C(=NH)NHOH, alkylC(=NH)NHOH, NHC(=NH)NH<sub>2</sub>,
alkylNHC(=NH)NH<sub>2</sub>, C(=S)NH<sub>2</sub>, alkylC(=S)NH<sub>2</sub>, C(=NH)alkyl,
alkylC(=NH)alkyl, C(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>), alkylC(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>);

R<sub>2</sub> is selected from H, chlorine, fluorine, bromine, iodine, OH, Oalkyl, amine, alkylaldehyde, alkylamide, alkylester, alkylketone, alkylacid, Oalkylamide, Oalkylacid, Oalkylester, aninealkylacid, aminealkylamide, aminealkylester, NC(=O)alkyl, NC(=O)aryl, NC(=O)cycloalkyl, NC(=O)alkylaryl, alkylamine, amide, aldehyde, ester, ketone, NO<sub>2</sub>, SH, S(O)<sub>n</sub>(C<sub>1-10</sub>alkyl), SO<sub>3</sub>H, SO<sub>3</sub>alkyl, CHO, acid, alkyl, C(=NH)alkyl, C(=NH)NHNH<sub>2</sub>, alkylC(=NH)NHNH<sub>2</sub>, C(=NH)NHOH, alkylC(=NH)NHOH, NHC(=NH)NH<sub>2</sub>, alkylNHC(=NH)NH<sub>2</sub>, C(=S)NH<sub>2</sub>, alkylC(=S)NH<sub>2</sub>, alkylC(=NH)alkyl, C(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>), alkylC(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>);

 $R_3$ ,  $R_4$ , and  $R_5$  are a hydrogen atom, alkyl group having 1 to 4 carbon atoms optionally interrupted by a heteroatom, or  $R_4$  and  $R_5$  are bonded to form - $(CH_2)_p$ -W- $(CH_2)_q$ -, wherein p and q are an integer of 2 or 3, a certain position on the methylene chain is unsubstituted or substituted by an alkyl group having 1 to 4 carbon atoms, W is a direct bond, - $CH_2$ -, -O-, - $N(R_6)$ -, or - $S(O)_r$ - wherein  $R_6$  is H or alkyl, and r is 0 or 1 or 2;

n is selected from 0, 1, 2;

X<sub>1</sub> is C or N;

X<sub>2</sub> is C or N;

X<sub>3</sub> is C or N;

X<sub>4</sub> is C or N; and

--- represents an optional additional bond when A is N.

Claim 3 (amended). A compound according to Claim 1 wherein the compound is according to Formula III

$$\begin{array}{c|c} & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ &$$

or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein A is B, G, J, K, L, and --- are as defined above.

Cancel Claims 4-13.

Claim 14 (amended). A compound which is:

7-Methoxy-1-(4-methoxy-phenyl)-3-p-tolyl-1H-quinoxalin-2-one.

Cancel Claims 15 and 30.

## **REMARKS**

Claims 1-3, 14, 16-29 and 31-32 are all the claims under consideration in the application. Claims 4-13, 15 and 30 have been cancelled. Attached are the amended claims labeled "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

A cross-reference to the parent application is added after the title. No new matter is added.

Applicants request prosecution of this application on the merits.

Respectfully submitted,

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Attachment - Amended claims, Version with Markings to Show Changes Made

HB1P4099.doc

# **VERSION WITH MARKINGS TO SHOW CHANGES MADE**

Claim 1 (amended). A compound according to Formula I

$$L \xrightarrow{X_3} X_4 \xrightarrow{A} D \\ X_2 \xrightarrow{X_1} F E$$

or stereoisomers or pharmaceutically acceptable salts, esters, <u>or</u> amides [or prodrugs thereof], wherein:

A is selected from [N, Nalkyl,] NCH<sub>2</sub>, N(alkyl)CH<sub>2</sub>, CH<sub>2</sub>N, CH<sub>2</sub>N(alkyl)[, NO];

B is selected from H,  $(C_{3-20})$ alkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, each optionally substituted with  $R_1$  and  $R_2$ ;

D is selected from H,  $(C_{3-20})$ alkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, each optionally substituted with  $R_1$  and  $R_2$ ;

E is absent or selected from O, S, NH;

F is selected from N, NCH<sub>2</sub>, CH<sub>2</sub>N;

G is absent or selected from alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl, cycloalkyl interrupted by one or more heteroatoms;

J is absent or selected from aryl or heterocycle each optionally substituted with  $R_1$  and  $R_2$ ;

- K is absent or selected from an alkyl, alkyl interrupted by one or more heteroatoms, cycloalkyl interrupted by one or more heteroatoms, cycloalkylalkyl interrupted by one or more heteroatoms, each optionally substituted with R<sub>1</sub> and R<sub>2</sub>;
- L is selected from H, chlorine, fluorine, bromine, iodine, OH, O(alkyl), amine, alkyl, fluoroalkyl, amide, NO<sub>2</sub>, SH, S(O)<sub>n</sub>(alkyl), SO<sub>3</sub>H, SO<sub>3</sub>alkyl, aldehyde, ketone, acid, ester, urea, Oalkylamide, Oalkylester, Oalkylacid, Nalkylacid, alkylamine, alkylamide, alkylketone, alkylacid, alkylester, alkylurea, Nalkylamide, Nalkylester, NC(=O)alkyl, NC(=O)aryl, NC(=O)cycloalkyl, NC(=O)cycloalkyl, NC(=O) alkylaryl, R<sub>1</sub>, R<sub>2</sub>, nitrile;
- R<sub>1</sub> is selected from H, amine, alkylamine, amide, C(=NH)NHNH<sub>2</sub>,
  alkylC(=NH)NHNH<sub>2</sub>, C(=NH)NHOH, alkylC(=NH)NHOH, NHC(=NH)NH<sub>2</sub>,
  alkylNHC(=NH)NH<sub>2</sub>, C(=S)NH<sub>2</sub>, alkylC(=S)NH<sub>2</sub>, C(=NH)alkyl,
  alkylC(=NH)alkyl, C(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>), alkylC(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>);
- R<sub>2</sub> is selected from H, chlorine, fluorine, bromine, iodine, OH, Oalkyl, amine, alkylaldehyde, alkylamide, alkylester, alkylketone, alkylacid, Oalkylamide, Oalkylacid, Oalkylester, aninealkylacid, aminealkylamide, aminealkylester, NC(=O)alkyl, NC(=O)aryl, NC(=O)cycloalkyl, NC(=O)alkylaryl, alkylamine, amide, aldehyde, ester, ketone, NO<sub>2</sub>, SH, S(O)<sub>n</sub>(C<sub>1-10</sub>alkyl), SO<sub>3</sub>H, SO<sub>3</sub>alkyl, CHO, acid, alkyl, C(=NH)alkyl, C(=NH)NHNH<sub>2</sub>, alkylC(=NH)NHNH<sub>2</sub>, C(=NH)NHOH, alkylC(=NH)NHOH, NHC(=NH)NH<sub>2</sub>, alkylNHC(=NH)NH<sub>2</sub>, C(=S)NH<sub>2</sub>, alkylC(=S)NH<sub>2</sub>, alkylC(=NH)alkyl, C(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>), alkylC(=NR<sub>3</sub>)N(R<sub>4</sub>)(R<sub>5</sub>);
- $R_3$ ,  $R_4$ , and  $R_5$  are a hydrogen atom, alkyl group having 1 to 4 carbon atoms optionally interrupted by a heteroatom, or  $R_4$  and  $R_5$  are bonded to form - $(CH_2)_p$ -W- $(CH_2)_q$ -, wherein p and q are an integer of 2 or 3, a certain position on the methylene chain is unsubstituted or substituted by an alkyl group having 1 to 4 carbon atoms, W is a direct bond, - $CH_2$ -, -O-, - $N(R_6)$ -, or - $S(O)_r$  wherein  $R_6$  is H or alkyl, and r is 0 or 1 or 2;

n is selected from 0, 1, 2;

X<sub>1</sub> is C or N;

X<sub>2</sub> is C or N;

X<sub>3</sub> is C or N;

X<sub>4</sub> is C or N; and

--- represents an optional additional bond when A is N.

Claim 3 (amended). A compound according to Claim 1 wherein the compound is according to Formula III

or stereoisomers or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, wherein A is [N or Nalkyl, and] B, G, J, K, L, and --- are as defined above.

Claim 14 (amended). A compound which is:

[7-Chloro-1-(3-dimethylamino-propyl)-3-phenyl-1H-quinoxalin-2-one;

7-Chloro-1-(3-dimethylamino-propyl)-3-phenyl-1H-quinoxalin-2-one;

3-(4-Chloro-phenyl)-7-methoxy-1-(4-methoxy-phenyl)-1H-quinoxalin-2-one;

2(1*H*)-Quinoxalinone, 7-methoxy-1,3-bis(*p*-methoxyphenyl);

3-(3-Chloro-phenyl)-7-methoxy-1-(4-methoxy-phenyl)-1H-quinoxalin-2-one;

 $3\hbox{-}(4\hbox{-}Fluoro\hbox{-}phenyl)\hbox{-}7\hbox{-}methoxy\hbox{-}1\hbox{-}(4\hbox{-}methoxy\hbox{-}phenyl)\hbox{-}1H\hbox{-}quinoxalin\hbox{-}2\hbox{-}one;$ 

3-(3,4-Dichloro-phenyl)-7-methoxy-1-(4-methoxy-phenyl)-1H-quinoxalin-2-one;

- 1-(2-Diethylamino-ethyl)-4-oxy-3-phenyl-1H-quinoxalin-2-one;
- 1-(2-Diethylamino-ethyl)-4-oxy-3-phenyl-1H-quinoxalin-2-one;
- 3-(2-Chloro-phenyl)-7-methoxy-1-(4-methoxy-phenyl)-1H-quinoxalin-2-one;
- 3-(4-Bromo-phenyl)-7-methoxy-1-(4-methoxy-phenyl)-1H-quinoxalin-2-one;
- 2(1*H*)-Quinoxalinone, 7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl;
- 7-Methoxy-1-(4-methoxy-phenyl)-3-(4-trifluoromethyl-phenyl)-1H-quinoxalin-2-one;
- 2(1H)-Quinoxalinone, 1-methyl-3-phenyl-, 4-oxide;
- 7-Methoxy-1-(4-methoxy-phenyl)-3-(3-trifluoromethyl-phenyl)-1H-quinoxalin-2-one;
- 7-Methoxy-1-(4-methoxy-phenyl)-3-p-tolyl-1H-quinoxalin-2-one
- 3-(2-Fluoro-phenyl)-7-methoxy-1-(4-methoxy-phenyl)-1H-quinoxalin-2-one;
- 1-(3-Diethylamino-propyl)-3-phenyl-1H-quinoxalin-2-one;
- 7-Hydroxy-1-(4-hydroxy-phenyl)-3-phenyl-1H-quinoxalin-2-one;
- 3-(4-Chloro-phenyl)-1-phenyl-1H-quinoxalin-2-one;
- 2(1H)-Quinoxalinone, 1,3-diphenyl;
- 1-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-phenyl-1H-quinoxalin-2-one;
- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-1-methyl-3-oxo-1,2,3,4-tetrahydro-quinoxalin-2-yl}-N-hydroxy-benzamidine;
- 3-{4-[5-(2,6-Dimethyl-piperidin-1-yl)-pentyl]-3-oxo-3,4-dihydro-quinoxalin-2-yl}-N-hydroxy-benzamide;
- 3-(3-Amino-1H-indazol-5-yl)-1-[5-(2,6-dimethyl-piperidin-1-yl)-pentyl]-1H-quinoxalin-2-one; or
  - 2(1H/)-Quinoxalinone, 1-[2-(diethylamino)ethyl]-3-[[4-(methoxy)phenyl]methyl]].